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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,417	01/07/2002	Michele Pagano	5914-090-999	1343

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	11

DATE MAILED: 09/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,417	PAGANO, MICHELE	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Acknowledgment is made of applicants election of the species of cks1 . The election was set forth to separate cks1 from p27. After review and reconsideration, the election of species requirement is withdrawn.

Claims 1, 4 and 7 were amended in the Paper filed November 20, 2002. Claim 7 has been amended by the Paper filed Jun 30, 2003. Claims 1-9 are pending and under consideration.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 29, line 11 and page 80, lines 6 and 10-12.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4 and 7 recite the limitation of "detecting a change in the activity of skp2". The metes and bounds of the activity of skp2 is not defined by the specification. The specification states that skp2 has ubiquitination ligase activity, and that skp2 associates with skp2-specific substrates and Skp2 interacts with cell cycle regulators such as p27. The claims are vague and indefinite as Skp2 has associations with numerous proteins within the cell as well as ubiquitin-ligase activity.

Claim 7 is vague and indefinite in the recitation of "phosphothreonine at position 187". SEQ ID NO:91 has two potential sites for phosphorylation of threonine, and it is not evident which site is position 187.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al in view of Lyapina et al (PNAS, 1998, Vol. 95, pp. 7451-7456, reference BN of the IDS submitted April 22, 2002) and Tsvetkov et al (Current Biology, 1999, Vol. 9, pp. 661-664, reference CW of the IDS filed April 22, 2002) and Yu et al, PNAS, 1998, Vol. 95, pp. 11324-11329).

Claim 1 is drawn to a method for screening compounds useful for the treatment of proliferate and differentiative disorders comprising contacting a compound with a cell or a cell extract expressing Cks1 and Skp2, or Cks1, p27 and Skp2, and detecting a change in the activity of Skp2. Claim 2 embodies the method of claim 1 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either p27 or Cks1. Claim 3 embodies the method of claim 1 wherein the change in the activity of Skp2 is detected by

detecting a change in the ubiquitination of p27 or degradation of p27 or Cks 1. Claim 4 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound in a purified system containing Cks1 and Skp2, or Cks1, p27 and Skp2, and detecting a change in the activity of Skp2. Claim 5 embodies the method of claim 4 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either p27or Cks1. Claim 6 embodies the method of claim 4 wherein the change in the activity of Skp2 is detected by detecting a change in the ubiquitination of p27 or degradation of p27 or Cks1. Claim 7 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound in a purified system containing Skp2 and one or both of a polypeptide corresponding to the carboxyl terminus of the human p27 chain having the sequence NAGSVEWTPKKPGLRRRQT (SEQ ID NO:91) with or without a phosphothreonine at position 187 and Cks1, and detecting a change in the activity of Skp2. Claim 8 embodies the method of claim 7 wherein the change in the activity of Skp2 is detected by detecting a change in the interaction of Skp2 with either the polypeptide or Cks1. Claim 9 embodies the method of claim 7 wherein the change in the activity of Skp2 is detected by detecting a change in the ubiquitination of the polypeptide or degradation of the polypeptide or Cks1.

Zhang et al teach that in transformed cells Shp1 (p19) exists in a complex with Shp2(p45) and Cks1 (p9) (column 2, lines 50-55). Zhang et al teach that the Skp1 polypeptide has the ability to regulate the cell cycle of a mammalian cell, and ability to modulate entry into S-phase, the ability to modulate the kinase activity of a cyclin-dependent kinase (column 3, lines 61-67). Zhang et al teach that the polypeptides of the inventions (p19 and p45) may function to modulate differentiation of cells or tissues (column 4, lines 7-8).

Yu et al teach that human Cul-1 is a member of the Skp1/Skp2 complex. Yu et al teach that the complex comprising Skp1/Skp2/Cul-1 is likely to function as an E3 ligase to selectively target cyclin D and p21 for the ubiquitin dependent protein degradation. Aberrant expression of skp1/Skp2/Cul-1 complex may contribute to tumorigenesis by regulating the level of G1 cell cycle regulators.

Lyapina et al teach that biochemical assays can be used to identify regulators of Cul-1 based SCF complexes to screen for modulators of the Skp1 and Cul-1 proteins.

Tsvetkov et al teach that phosphorylation of p27 at Threonine 187 was essential for the degradation of p27 and that SCFskp2 specifically targets p27 for ubiquitination and degradation thereby during the cell cycle progression.

It is noted that Cks1 is not defined by the specification in terms of Sequence, and many proteins have more than one name by virtue of their having been discovered by different labs. It appears as if the human Cul-12 protein is the same as the Cks1 protein as it exists in the same complex with Skp1 and Skp2 as taught by the specification, and as it is part of the SCF ubiquitin ligase complex controlling the entrance into the S phase of the cell cycle. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to screen compounds for the treatment of proliferative and differentiative disorders comprising contacting a compound with a cell or a cell extract expressing Cul-1 and Skp2, or Cul1, p27 and Skp2 and detecting the degradation of p27 or cell cycle progression or inhibition.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Yu et al on the contribution of the Skp1/Skp2/Cul-1 complex on tumorigenesis, the teachings of Tsvetkov et al who correlate the degradation of p27 with the ubiquitination by SCFSkp2, and Lyapina et al who suggest that biochemical assays can be used to identify regulators of Cul-1 based SCF complexes in screens for modulators of skp1 and Cul-1 proteins. One of skill in the art would be motivated to find said compounds in order to treat malignant cells.

All claims are rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/21/03